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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,024	09/07/2001	Gerald Wayne Becker	X-12799	9679

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EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 12/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,024	BECKER ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5/1/03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claim Rejections - 35 USC § 102

1. Claims 21-34 are pending in the instant application. Claims 1-20 have been canceled and claims 21-34 have been added as requested by Applicant in the Paper filed Nov. 24, 2003.

Priority

2. Applicants' amendment to the specification to recite the priority claimed in the declaration is acknowledged.

Specification

3. The disclosure is objected to because of the following informalities: Figures 1 and 2 have been removed from the specification as requested by Applicants, however the specification contains references to the now removed figures (page 74, Example 5, page 81, Example 11).

Appropriate correction is required.

Withdrawn Rejections

4. Any rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 21-34 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 21-34, as written, do not sufficiently distinguish over the proteins or nucleic acids as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. See *Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "isolated" or "purified". See MPEP 2105.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6.1 Claims 29 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a FLINT analog consisting of residues 1-218 of SEQ ID NO: 1 or residues 1-247 of SEQ ID NO: 3, does not reasonably provide enablement for a FLINT analog comprising one or more conservative amino acid substitutions wherein the analog retains anti-apoptotic activity in vivo or in vitro. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant application discloses that the FLINT protein is proteolytically cleaved in vivo to produce at least two major peptide fragments, and that the protein fragment having residues 1-218 of SEQ ID NO: 1 retains FAS Ligand or LIGHT binding activity. However, because these claims encompass proteins that can have one or more conservative amino acid substitutions, and only one naturally occurring polypeptide has been disclosed in the instant specification, a practitioner can not make a protein comprising an amino acid sequence other than the one disclosed in the instant specification and expect it to have the same functions. There is no limit on the number of conservative amino acid substitutions that may be made. There is no identification of the amino acid residues which would be common to FLINT proteins and which would not. Specifically, the instant specification does not identify those amino acid residues in the amino acid sequence of SEQ ID NO: 1 which are essential for its biological activity and structural integrity and those residues which are either expendable or substitutable. In the absence of this information a practitioner would have to resort to a substantial amount of undue experimentation in the form of substitutional mutation analysis of residues before they could even begin to rationally design a functional fused protein having other than a natural amino acid sequence. The disclosure of a single polypeptide with a natural amino acid sequence is clearly insufficient support under the first paragraph of 35 U.S.C. § 112 for claims which encompass variants encompassed by the claims.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions

within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity.

The current claim limitations are analogous to those of claim 7 of U.S. Patent Number 4,703,008 which were held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement in *Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd.*, 18 U.S.P.Q. 2d, 1016 (CAFC, 3/5/91, see page 1026, section D). In that instance, a claim to a nucleic acid encoding a polypeptide having an amino acid sequence sufficiently duplicative of the amino acid sequence of erythropoietin (EPO) so as to have a specified biological activity was held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement.

The disclosure upon which that claim was based described a recombinant DNA encoding EPO and a few analogs thereof. That disclosure differs from the instant specification because, whereas the instant specification describes a naturally occurring protein, it does not describe even a single variant thereof. The court held that what is necessary to support claims of this breadth is a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. For proteins, that means disclosing how to make and use enough sequences to justify the grant of the claims sought. As indicated, the instant specification is even more limited than the '008 patent because it describes only a single protein and no analogs or mutants thereof and, therefore, provides even less support than the '008 specification for claims of comparable scope and which were held to be invalid in that patent.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

For the reasons discussed above, due to the large quantity of experimentation necessary to generate the large number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples and written description directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and

the breadth of the claims which fail to recite any specific functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The current claim limitations are analogous to those of claim 7 of U.S. Patent Number 4,703,008 which were held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement in *Amgen Inc. v. Chugai Pharmaceuticals Co. Ltd.*, 18 U.S.P.Q. 2d, 1016 (CAFC, 3/5/91, see page 1026, section D). In that instance, a claim to a nucleic acid encoding a polypeptide having an amino acid sequence sufficiently duplicative of the amino acid sequence of erythropoietin (EPO) so as to have a specified biological activity was held to be invalid under 35 U.S.C. § 112, first paragraph, for want of enablement. The disclosure upon which that claim was based described a recombinant DNA encoding EPO and a few analogs thereof. That disclosure differs from the instant specification because, whereas the instant specification describes a naturally occurring protein it does not describe even a single variant thereof. The court held that what is necessary to support claims of this breadth is a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. For proteins, that means disclosing how to make and use enough sequences to justify the grant of the claims sought. As indicated, the instant specification is even more limited than the '008 patent because it describes only a single protein and no analogs or mutants thereof and, therefore, provides even less support than the '008 specification for claims of comparable scope and which were held to be invalid in that patent.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6)

breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

It is acknowledged that the level of skill in the art is high. However, for the reasons discussed above, due to the large quantity of experimentation necessary to generate the large number of derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any specific functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

6.2 Claims 29 and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification describes a polypeptide sequence consisting of amino acids 1-218 of SEQ ID NO: 1, which is the proteolytically processed FLINT protein without signal sequence, and polypeptide consisting of amino acids 1-247 of SEQ ID NO: 3, which is the proteolytically processed FLINT protein with the signal sequence, and shown to have the following activities: binding FAS Ligand and LIGHT, and having anti-apoptotic activity. However, the claims as written include polypeptides comprising homologues, encompass polypeptides that vary substantially in in amino acid composition. The instant disclosure of a the single naturally

occurring polypeptide with the instantly disclosed specific activities, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606."

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated

polypeptide sequence SEQ ID NO: 3. Protein function, however, cannot be reliably predicted from protein sequence homology. For example, Transforming Growth Factor (TGF-beta) Family OP-1 induces metanephrongenesis whereas closely related TGF-beta family members-BMP-2 and TGF-beta1-have no effect on metanephrogenesis under identical conditions (Vukicevic et al., 1996, PNAS USA 93:9021-9026). Platelet-derived Growth Factor (PDGF) Family VEGF, a member of the PDGF family, is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells while PDGF is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (Tischer et al., U.S. Patent 5,194,596, column 2, line 46 to column 3, line 2). Finally, vertebrate growth hormone of 198 amino acids becomes an antagonist (inhibitor of growth) when a single amino acid is changed (Kopchick et al, U.S. Patent No. 5,350,836). Even 99% homology does not allow predictability in this instance. Given the unpredictability of homology comparisons, and the fact that the specification fails to provide objective evidence that the additional sequences are indeed species of the claimed genus it cannot be established that a representative number of species have been disclosed to support the genus claim. The instantly claimed genus is not so limited and the prior art does not provide compensatory structural or correlative teachings to enable one of skill to identify the polypeptides encompassed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7.1 New claims 23-28, 31-34 are rejected under 35 U.S.C. 102(a) as being anticipated by Masiakowski et al., WO 99/07738, Feb. 18, 1999, Pitti et al., Nature, Vol. 396, pages 699-703, December, 1998, Emery et al., US Patent No. 5,885,800, March 23, 1999, Gentz et al, WO 98/30694, July 16, 1998 or Emery et al., EP 0 861 850, Sept. 2, 1998, cited in the previous office action.

Claims 23-28, 31-34 encompass a FLINT analog wherein the analog comprises residues 1-218 of SEQ ID NO: 1 or residues 1-247 of SEQ ID NO: 3, wherein said analog has a lower binding affinity for FASL than FLINT, or wherein said analog has a binding affinity for LIGHT about the same as the binding affinity of FLINT for LIGHT, and nucleic acid sequence that encodes residues 1-218 of SEQ ID NO: 1 or comprises residues 1-654 of SEQ ID NO: 2.

WO 99/07738, Pitti et al., US Patent No. 5,885,800, WO 98/30694 and EP 0 861 850 each disclose a polypeptide comprising 300 amino acids, which is identical to the polypeptide of SEQ ID NO: 3 and identical to SEQ ID NO: 1 of the instant invention over the 271 amino acids of SEQ ID NO: 1, and nucleic acid encoding the proteins and identical to nucleotides 1-654 of

SEQ ID NO: 2 of the instant application (see attached sequence alignments). Although each of these references did not appreciate that the full length polypeptide of SEQ ID NO: 1 or 3 undergoes proteolysis in vivo to produce at least two major peptide fragments (amino acids 1-218 and 219-271 for SEQ ID NO: 1 and amino acids 1-247 and 248-300 of SEQ ID NO: 3), the claims as written read on the larger polypeptide, which is disclosed in each of the references. The claims that recite a specific activity (claims 27, 28, 33 and 34 are also rejected, because the claims as written do not have the limitation that the analog is isolated or purified, and therefore read on the naturally occurring fragment present in vivo, and the recited activities are inherent activities of the fragments. Therefore, each reference anticipates the claims.

Claims 21 and 22 are not included in the rejection, because it was not known that these specific fragments were proteolytically cleaved, and the claims are drawn to a FLINT analog consisting of those specific residues recited in the claims.

7.2 New claims 23-28, 31-34 are rejected under 35 U.S.C. 102(e) as being anticipated by published US Application No. 20020150583, priority date January 14, 1997 (60/035,496), cited in the previous office action.

Application No. 20020150583 discloses a polypeptide (SEQ ID NO: 2) comprising 300 amino acids, which is identical to the polypeptide of SEQ ID NO: 3 and identical to SEQ ID NO: 1 of the instant invention over the 271 amino acids of SEQ ID NO: 1, and discloses a nucleic acid sequence (SEQ ID NO: 1 of which nucleotides 112-678 are 100% identical to nucleotides 1-654 of SEQ ID NO: 2 of the instant application. Although this reference did not appreciate that the full length polypeptide of SEQ ID NO: 1 or 3 undergoes proteolysis in vivo to produce at least two major peptide fragments as described above, the claims as written read on the larger

polypeptide, which is disclosed in the reference. The claims that recite a specific activity (claims 27, 28, 33 and 34 are also rejected, because the claims as written do not have the limitation that the analog is isolated or purified, and therefore read on the naturally occurring fragment present in vivo, and the recited activities are inherent activities of the fragments. Therefore, Application No. 20020150583 anticipates the claims.

Claims 21 and 22 are not included in the rejection, because it was not known that these specific fragments were proteolytically cleaved, and the claims are drawn to a FLINT analog consisting of those specific residues recited in the claims.

Conclusion

8. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM. ***Applicant is advised that effective January 23, 2003, the Examiner's phone number will be (571) 272-0878.***

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564. ***Applicant is advised that effective January 23, 2003, Yvonne Eyler's phone number will be (571) 272-0871.***

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

Eileen B. O'Hara

Patent Examiner